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Sir John Vane FRS in interview with Max Blythe

Oxford, 24 February 1988

Part One

MB Sir John, your life began in Birmingham. Can you tell me about early days, about Mum and about Father? Those were interesting times.

JV Well, I was born just outside Birmingham, in a little village called Holywood after which I suppose the American Holywood was named. I was brought up in the suburbs of Birmingham in a place called Hall Green and went to the local primary school and then went on to the King Edward's High School for Boys, which was the top school foundation there. My mother was from farming stock. She came from Malvern in Worcestershire and my father was brought into the country as an immigrant from Russia at a very early age and then lost touch with his parents, so I don't know very much about his family.

MB But he was a fascinating man.

JV Oh yes, he was a fascinating man.

MB Can you tell me something about him and about Mother?

JV He was a carpenter and he worked himself up into a small business making greenhouses and garden sheds and I suppose I remember him best during the war as an air-raid warden, busy as an air-raid warden and then as a… what do you call them? – a supernumerary policeman.

MB A special policeman?

JV Yes.

MB So he was a very active man.

JV Yes he was an active man. They gave me a small chemistry set for a Christmas present when I was about eleven or twelve and I was very happy doing chemistry experiments with test tubes and using my mother's gas stove as a Bunsen burner, until one day I was making a stink bomb and it blew up and spoilt all the paint on the wall which my father had just very carefully done, and so he very wisely built me a shed in the garden, a wooden shed, and that became my first laboratory. He fitted it out with gas and with water and I was able to do experiments in there – all the kind of experiments young boys like to do, like making alcohol and making stink bombs, and making fireworks, and making little cannons out of old bullets or old cartridge cases.

MB That was a tremendous luxury for a boy of that age. I mean, it was terrific to have a father who supported you that much.

JV Yes, I spent most of my time in the shed, in the laboratory so to speak; it was my first laboratory and it was a great help to me. I began to accumulate chemical apparatus. I began to get retorts and all the exotic things that young people liked, and I suppose, looking back on it, it was not really chemistry I was interested in, it was experimentation. It was the only outlet I had as an experimentalist. Nevertheless, it became a big hobby. It was my main hobby and with the boy next door, Alan Young, we also wrote a little newspaper between us, which we circulated to our parents and other friends, typing it out in the same shed.

MB This must have been an exciting time and you obviously had the support of both parents. Did they feel that you were going to be a scientist? Was this a wish of theirs as well? Did you feel that they supported you to the point of, you know, the future?

JV Yes, they were very keen for me to be a scientist of some sort, very keen for me to do my homework. And my father actually wanted me to be an electronic engineer and the words were very new in those days. He was probably right, I should have been an electronic engineer. But that was his vision of the future and that was in 1939, 1940.

MB That wasn't bad was it? That was quite good vision.

JV Yes. In 1939 when the war started, we were evacuated as a school to Repton in Derbyshire and I was billeted on to one of the language masters at Repton and his family, and that had quite an influence on my life. I was there for three to five months, living with quite a different kind of family, because they were academic and my own parents were more practical and business-like. So that was also an interesting interlude in my life, and to live in the country was a change also.

MB It's a terrific bit of countryside round there, isn't it?

JV Yes. We went for long walks and joined the Cubs and the Scouts and so on. And then, going on in the country aspect, after we went back to Birmingham – there were no air raids while we were away – and we went back after about five months, when the air raids started, but each summer I used to go off to camp to pick apples or to pick hops and that was also a very exciting experience to be away from school, away from parents and to live in tents.

MB So very early on… this kind of…the experimental person and the country lover, both these patterns were beginning to forge.

JV They were beginning to forge then, yes.

MB Did you keep contacts with Repton by the way?

JV I did for a long time. The daughter of the family, called Betty, who was a girl who was very attractive. She was one of my… she was the first person I fell in love with at the age of about eight or nine or ten, or whatever it was – eleven, I think – and we kept contact. She became a nurse in London and then we lost contact, and in 1982 when the prize [Nobel Prize] was announced I had a letter from Betty Darville(?), saying, 'Are you the John Vane who was billeted with the Topliss'(?) in Repton.' And so we made contact again and her parents were still alive and we had a marvellous lunch together and went over old times. A man, I suppose, who inspired me most at school was a man called 'Perkie' Lambert – he was a well-known textbook author.

MB Mr J Lambert who wrote with Holderness.

JV That's right, yes, a school textbook. He was a marvellous teacher and he clearly turned me on as far as experimental sciences went. He used to do experiments in front of the class – demonstrations – and he used to come round and talk to us while we were doing the experiments. So it was natural for me to go on to Birmingham University, which was just across the road from King Edward's High School, and to do chemistry there, which I did, during the war. And then I found that I wasn't really very interested in chemistry, it turned out to be a sort of recipe making science.

MB So there was no continuity with the kind of spirit that 'Perkie' Lambert had created.

JV Not at all. The main emphasis in the practical classes – and clearly I was then interested in the practical side of things and the experimental side of things – the main interest was whether you got a 60 per cent yield, a 70 per cent yield or a 90 per cent yield.... and working to a recipe. It was no longer experiments. As a young person you do experiments but you don't know how they are going to come out; you don't know whether you are going to have an explosion or whether it is going to work or not.

MB But this became stultifying.

JV This became stultifying – kitchen recipe stuff. So I began to lose interest in chemistry and the chemistry professor then, a man called Maurice Stacey, who was famous for his sugar work, called me into his office one day and said, 'Well Vane, what are you going to do when you leave?' And I said, 'Anything but chemistry.' I don't think it surprised him very much. I think he had noticed my disinclination. And he said, 'Well, I've got a letter on my desk from a man in Oxford, a man called Harold Burn.[1] I sent someone to him last year, a man called Bob Stephenson, who was a student like you here to train in pharmacology, and he is looking for somebody else now. He wants a young man from my laboratory to train in pharmacology. Would you like to do that?' And immediately I said 'Yes.' The idea of going to Oxford was

[1] Joshua Harold Burn, Professor of Pharmacology, Oxford University, 1937-59.

incredible. Then I went off afterwards and looked up what the word pharmacology meant, because I had no biological training, and found out what it meant and went to Oxford, met with Bob Stephenson who was a year older than I was. He showed me the kinds of things he was doing and it looked fascinating, so I went to Oxford.

MB That moment with Stacey though – Maurice Stacey – was quite a key moment in the career, wasn't it? He must have recognised that it was right for you to move across at that stage and come to Oxford. That must have been quite perceptive on his part. The influence has been enormous.

JV The influence was enormous. It changed my whole career. I haven't talked to him about it since. I doubt whether he would remember me. I think he's still alive, but it would be interesting to see if he did it because the letter happened to be on the desk, or whether he'd done it to half a dozen other people as well, but clearly it changed my whole direction from going... I was even thinking maybe my father was right, maybe electronic engineering was the best thing to do.

MB Sir John, before we actually come to Oxford, we said quite a bit about Father, but we haven't said quite as much about Mother, in fact, relatively little. Could we take her into the story a bit more now, before we come to Oxford? She was ever so supportive, tell me a little bit more about her.

JV Yes. She was a very comfortable person, a fairly large lady full of smiles and always calming down the house rather than stirring it up. I had a brother and a sister, both older than I was, but they both went off to the war, so I spent a lot of time at home with my parents by myself. And when I used to get into arguments with my father, which happened quite often, my mother would be the peacemaker, and she would slip me the odd shilling or so when I needed the money. But she was a very simple and wise lady and very well liked by all the neighbours and contributed, I think, considerably to the fact that I can sit fairly calmly here and talk to you now, rather than feeling nervous.

MB Both parents must have felt remarkably good about the chance for you to come to Oxford at that stage, that must have been very exciting for them.

JV Yes, they were thrilled by it and came to see me in Oxford quite often. And I used to have a little Corgi motorcycle, with tiny wheels. I drove it home one weekend to Birmingham – that was terrible. It was only about sixty miles, but to be exposed on this little machine for sixty miles… and my father very kindly putting it in the back of his car and driving me back again. So my mother had a big influence also, she was the solid home figure who kept the place together. The boy next door was also a very close friend. His mother was a pianist. She always opened her piano practice – it was a semi-detached house – it came striding through the walls, *In a Country Garden.* So that became a tune which I never want to hear again. Three or four times a day she would start practising. She tried to teach me the piano but without any success. I wasn't of that ilk.

MB These were interesting days. You went to Oxford. What happened in the early days at Oxford? Who did you make contact with and [who] directed your studies there? Was that an exciting time? You had come to work with Burn.

JV I came to work with Joshua Harold Burn. He was a very influential person in my life. He was very stimulating and he was also… had a fairly short temper and he was able to make you do the things he wanted you to do by a little fear of him. But he was the first person, apart from 'Perkie' Lambert, who began to teach me scientific method. He had lunch parties every day in the Department of Pharmacology and he'd sit at the head of the table and there'd by [Hermann] Blaschko,[2] [Edith] Bülbring and [Raymond] Ing, who was the chemical pharmacologist there, and John Walker and many other people who are now retired, sitting round the lunch table, and we'd have a conversation directed by Harold Burn on things that had nothing to do with pharmacology but just to do with what was in *The Times* newspaper. I remember Hermann Blaschko saying he didn't understand why *The Times* spent so much of its paper on reporting business affairs, why didn't it report academic affairs instead, just a little bit on academia and five pages on business. So it was in that department that I began to learn biology and I began to learn scientific method. And about a month after I got there, Burn called me into his office and said, 'Vane it's not good enough.' he

[2] Hermann Karl Felix Blaschko was born in Berlin in 1900. He adopted the name Hugh when he came to England.

said, 'You're not doing well enough, you've got to do better.' Now he didn't define what I had to do better in. I just had to do better, and then I found out that this was a regular occurrence. He probably made a note in his diary saying, 'Next month tell Vane, or tell Gardi(?), or tell Stephenson... he's got to do better', because we all had it, everybody had it.

MB A regular spur.

JV A regular spur, yes, and never with a particular definition of what you had to do better in, and it worked, you did better.

MB Yes, and you also moved ahead.

JV He was a strict taskmaster. He was a very professional man. He would not let you give a paper at a meeting. I remember the first paper I ever gave at a scientific meeting, I had a cold and lost my voice the day before, probably through an attack of nerves as well, and he said, 'Rubbish', you'll be giving it and you'd better come and rehearse it for a fourth time in the lecture theatre now, just to make sure you know what you're going to say.' He rehearsed with everybody very rigorously and I do too also – rehearsals before giving a ten minute paper are a must in my area of science.

MB This is terrific background though, isn't, that you were being supplied with by Burn and as you say you've carried this tradition on.

JV Yes. He was carrying it on from Dale. He was one of Dale's students and I... sometimes when I lecture on the sort of history of my life and the pharmacology, I describe myself as a sort of scientific grandchild of Dale, fathered by Burn. He was a very active man and every Thursday Harold Burn would do a heart-lung preparation in a dog, and the technician then, the head technician, was a man called Harold Ling – who was a super guy and as graduate students, Bob Stephenson and I used to go and play bridge with Ling and his wife, once a week, in the evening – but on a Thursday the lab was full of bustle because Burn was going to do his heart-lung prep in a dog, and you weren't allowed in the room unless you had something to do in there because it was a distraction. And John Walker, who I saw recently at a dinner, coined a phrase

that if it was a successful preparation it was called heart-Ling preparation and if it was unsuccessful it was called a heart-Burn preparation.

MB Terrific. What problem did Burn have you to work on?

JV Well, he treated me in the same way that he treated most of the young people who came to him who had little or no experience. He gave them a drug, a new drug that had come to the market or was coming to the market and said, 'Tell me about the pharmacology of this drug.' He gave me a substance called Paludrine which was an anti-malarial just about to be marketed by ICI [Imperial Chemical Industries] – had just been marketed – and this meant that you put it through twenty or thirty different pharmacological methods to find out what it did and it meant that you learnt all of those methods. And, in point of fact, we found it did some interesting things which it wasn't supposed to do, which helped us to work out the role of acetylcholine in the heart, which was fortunate. So he gave this as an arbite(?). I did my BSc thesis on the pharmacology of Paludrine and then went from there to Sheffield to work with Derek Wood, who had been in Burn's department, had recently moved up there as a lecturer or senior lecturer in pharmacology, to work with him.

MB Was that a good move?

JV It was a stark contrast to the Oxford laboratory. In Sheffield the laboratory space was much more dishevelled. I had a tiny little office in a corner, a triangular office. Derek Wood was doing a lot of teaching and not very many experiments. It was the first time I had been in a department which had concentrated on teaching rather than research. And the professor was hardly ever there – he was a clinical man – and so I found it fairly lonely in trying to do my own experiments without much discussion with other people.

MB What had you taken there to do? Had you taken some of your work...?

JV I had taken some perfusion equipment with me and I began to perfuse stomachs in cats to find out things about the blood flow. Hans Krebs was in Sheffield at the

same time and he had as his student Hans Kornberg and we became friends, and I saw him a few weeks ago also.

MB That was pretty powerful stacking wasn't it, in terms of top scientists for Sheffield?

JV Hans Kornberg was the only one and he moved back to Oxford I believe, or Cambridge, I can't remember which he went to first. Kornberg, of course, is now in Cambridge as Master of… which college is it?

MB Christ's.

JV Christ's, that's right, yes, I think. So I went to Sheffield. I spent about six to eight months there and then went to a meeting of the Pharmacological Society and saw Geoffrey Dawes, who I knew from his sojourn in Burn's department, and he had just become Director of the Nuffield Institute for Medical Research in Oxford, which was then in the Tower of the Winds [the Radcliffe Observatory]. And I chatted with him and told him that I was missing the intellectual stimulation and asked him whether he might take me on as a PhD student, which he did. So I moved back to Oxford after about ten months in Sheffield and we lived around and about. By that time I was married and Daphne my wife was pregnant, and she trudged around looking for places to live and she came across the Ferry [Marston Ferry Road(?)] one day to Marston and met a chap called Norman Heatley, and Norman and Mercy were looking for somebody to act as a sort of live-in cook in return for a couple of rooms at cheap rent, in return for my wife cooking the meals three or four times a week. And so we moved in there, in Old Marston and had a very happy time there. I got to know them both very well. Norman is a magnificent man, he really is, and we became very firm friends. He has a workshop in the garden and he makes all sorts of interesting gadgets for the house, in his workshop. Then we moved down to the Abingdon Road to live with John Widdecombe(?) and his wife, who had just bought a house down there, for about a year and then we moved to a little tiny cottage up in North Oxford, Hernes Road, I think it was called. Is there a South and a North Hernes Road?

MB I think that's right.

JV The cottage was owned by a lovely little old lady who had a big house next to it. It was in her garden, it was a sort of groom's cottage. We had a very happy time there, also. Our first child was born when we were with the Heatleys and our second girl was born when we were in that cottage.

MB That was about 1951?

JV That was about 1951, yes. The first was born in 1949.

MB And your D Phil was also finished about that time.

JV It was finished about 1952, '53, yes.

MB What did Dawes supervise in terms of the D Phil? What was the work that brought you back?

JV Well he was interested in the way in which the heart beat. He was interested in the refractory period in between beats, and in measuring the electrical happenings in the heart, and so I very happily joined him on that and on the mode of action of quinidine and of other drugs which affect the heart. At the same time I was developing my own perfusion apparatus for perfusing cats' stomachs and measuring the secretion of acid in the stomach when it is stimulated by histamine and trying to find out whether histamine had a direct or indirect action. Interestingly, a couple of people came into my life during that period. One of them was Dharam(?) Singh (?), a Sikh from India who then became, many years later, the Director of the Ciba Geigy Laboratories in India, first of all Ciba Laboratories. He became a very firm friend. I remember the surprise I felt when our heads clashed over the operating table once, at the hardness of his turban. I hadn't realised it was so full of hair, it was rock firm. The other man was Gustav Born who went on to become 'Mr Platelet' of this county and has become famous in the area of platelets. We did some work together on histamine and gastric secretion. So my D Phil thesis was a sort of combination of those two projects. Geoffrey Dawes himself had then moved on to become interested in the neonatal

conditions and in physiology of the birth process and was working on sheep, pregnant sheep.

MB There was enormous tribute paid to him by two or three people who have been part of this series of interviews, people like [Sir] Peter Tizard. He seems to have had such a great effect; it is nice to have him mentioned.

JV Yes. He was a very stimulating person also, quite different from Burn. He didn't blow up as quickly as Burn did. You could always tell when Burn was about to have a fit because his neck began to go red and you knew something was on the way. There was one occasion when he was showing a visitor around – I don't think it was Linus Pauling, Linus Pauling came to the labs one day. Burn had a great reputation among visitors. He used to go up to a visitor in the hallway and shake him by the hand and say, 'Now, have you met me before?' which used to put the visitors off. This was an American visitor and I was sitting at the desk working with a little piece of apparatus in which we put a mouse and we put electrodes across its tail to try and measure analgesia and we were looking to see whether we could measure analgesia after aspirin, which nobody could do in those days and which I couldn't do either. But, there was one little pellet of mouse dung on the apparatus and I could see Burn's neck going red as he took the visitor away, and lo and behold, when the visitor had left, half an hour later he came storming back. He said, 'This place is in a disgusting mess,' and he had me, all of the graduate students Edith Bülbring, Hugh Blaschko, Raymond Ing, all cleaning the place up and polishing benches, because he thought it was all too dirty. And that was concentrated on that one piece of mouse pellet which was sitting there. Dawes was quite different. He didn't have these explosions at all. He was also fairly far-sighted in being able to see which way experiments were going. He spent two or three days a week doing experiments on pregnant sheep, and it was of course during the period of meat rationing and so, at the end of the experiment somebody, and it happened to be me most of the time because I was the youngest PhD student there, was designated to carve the carcass of the sheep up and distribute it amongst the hungry people in the lab. We found out that the Home Office regulations determined that the thing had to be burned at the end of an experiment, but they did not say how much, so we regarded cooking as okay. And we also found out that the anaesthetic that was used didn't survive the cooking process. I remember the look of astonishment on my

mother's face when they came to see us one weekend and we brought out a 5lb leg of lamb. She didn't really understand how we were able to do this with meat rationing on. So that gives you a flavour of the atmosphere in the Nuffield Institute for Medical Research. There were experiments going on on the refractory period of the heart. Joan Mott was there. She was still doing experiments on the physiology of the eel and she had eels around and she killed the eels by cutting off their heads and putting them into formalin. And for the next... what seemed like several hours the eel's head would go on gasping for breath in the formalin. It still had these reflex movements. Joan Mott was there, several other people and Geoffrey became more and more interested in gadgetry which would enable him to measure blood flow in the foetus and in the sheep, so there was a man there skilled in making new flow-meters and he developed a new flow-meter, an electronic flow-meter. Gordon Ardran was there, the radiologist, and he was doing radiological work. Peter Daniels was there doing his physiology. So it was a very stimulating laboratory. At the same time as doing research there, because of my relationship with Burn, he had invited me, as he invited other people in the Nuffield Institute, to go across to his lab and act as a demonstrator to the medical students and that was great fun, too. It was my first experience of on-hands teaching people in practical classes. It was during that period that I met a man called Arnold Welch who had come over from Cleveland, where he was professor of pharmacology in Case Western Reserve University, to do a sabbatical six months with Hugh Blaschko, and Arnold was a very enthusiastic man, and still is. And towards the end of his six months he asked me whether I would like... he was then moving from Cleveland to New Haven to go and take up the new position of professor of pharmacology and chairman at Yale University School of Medicine, and he asked me whether I would like to go and join him there for a year or two, and we decided we would. He was a biochemical pharmacologist and he said, 'I've already appointed ten or twenty biochemists who are going to do biochemical pharmacology, what I want is somebody trained in classical pharmacology just to add balance to the department.'

MB Get the kymographs in there.

JV That's right. So I ordered all the kymographs and things here before I left. They're now in a museum in New Haven. They rapidly became museum pieces.

MB Was Yale a great opportunity place for you? Did that really set seeds that were going to have long-term importance?

JV I suppose it did, yes. It opened our eyes enormously to other worlds. Before I went I was very anxious as to whether I'd get another job back in this country. I talked to Edith Bülbring and I talked to Burn, I talked to all of my mentors and they all said, 'Well, all you have to do is to do some good work and you'll get a job,' and so I was encouraged by that. The atmosphere at Yale was quite different from that in Oxford or in Sheffield or in the Nuffield Institute – rather a more closed atmosphere simply because of the characteristic of the laboratories. They were all arranged down one long corridor and if you wanted the door of your laboratory open you had to prop it open. And many people propped the door open, but some of them didn't and so immediately it became a little more segregated. We all met for lunch as we did in Oxford. I think Arnold Welch learned that from Burn, to have a lunch gathering. And I learned a lot more about biochemistry there. I learnt a different attitude towards science, a more cellular attitude towards science, and I took to them an attitude of trying not to break up cells, trying to keep organs alive, trying to keep animals alive rather than looking at individual broken cell. So it was an interesting period. I met a lot of American scientists, especially at the FASEB [Federation of American Societies of Experimental Biology] meetings which were then going, I think, once a year in Chicago or Atlantic City, and we formed a lot of firm friendships there. We took an apartment in a three level house. We were in the middle apartment and very soon after that, Dick Barlow and his wife came to Yale to work with Arnold Welch. He was a chemical pharmacologist. And they took the bottom apartment when it became free. And then I met after a few months a young doctor called Denis Abelson, who had just got married and come to Yale, who was also looking for an apartment and the upstairs apartment became free. So Dennis and his wife Plum(?) came to live there. So it was a sort of British house and we had lots of good parties and lots of interactions between us. It was owned by a man called Mr Golden(?), who was an alcoholic, who used to arrive every evening – several evenings – at about 5-6 o'clock and it became a game as to who could not offer Mr Golden a drink and get him out as quickly as possible. He was the local sheriff and he had a partner in a law firm, who ran the law firm, and his partner was a Democrat and he was a Republican. He said, 'It's very simple: when the Democrats get in my partner becomes the sheriff and when the Republicans get in, I

become the sheriff and my partner runs the law business.' We had a park opposite the house where Daphne took the two young girls to play on the swings and things. The American life, we learned, was very much more open air than the British life we had been accustomed to. You went for picnics because you could rely upon the weather, and you went to the beach, and you went to the beach most weekends – had picnics on the beach – and you went to friends' houses and had barbecues in the garden. And so we began to live a much more outdoor life in the two years that we were at Yale. And we made may other friends: Laszlo Leichter(?), who came from Hungary to England many years ago – probably just after the Second World War in 1946 – became a good friend. He came out to Yale to work with Arnold Welch. Bernard Langley(?), who is now at ICI, also came out to work with him, so there was quite a strong British contingent out there.

MB This was great meeting place, a great centre. What about the work? Did the work justify the visit in addition to the meetings?

JV I set up, as Arnold Welch had asked me to, classical pharmacology. I took on a couple of his graduate students and taught them classical pharmacology and we got several papers out. Bill McMillan(?) was one of them and he worked on the effects of histamine on skeletal smooth muscle. Histamine doesn't have much effect on skeletal smooth muscle, but he managed to see an effect which he traced down to a rise in blood potassium caused by histamine, so that was quite interesting. Yes, the work panned out OK. And towards the end of the period when I was beginning to look for... Arnold Welch wanted me to stay there. He said, 'Stay on,' he said, 'Take a medical degree.' I said, 'Well, I'm doing fairly well without a medical degree.' 'Ah, but if you really want to make progress in pharmacology,' he said, 'you really need a medical degree and can stay on here and take it and do your research part-time at the same time.' But I turned that down. I sometimes remind him of that when I see him nowadays. And I began to look for jobs back here and had several offered to me. Gladwin Buttle was then at the School of Pharmacy and he wanted a man to become a senior lecturer and offered research opportunities, but also you had to contribute to the teaching programme with teaching the pharmacists and the nurses and about ten different classes, and it was quite clear that was a teaching rather than a research job. Then Bill

Paton[3] also got in touch with me. Now, that was quite a different kettle of fish because Bill had by that time moved to become the new professor of pharmacology in the Royal College of Surgeons, in what was then called the Institute of Basic Medical Sciences and that was housed outside the College of Surgeons at the towers on the top of the Examination Hall in Queen's Square, in the attic of Examination Hall. And he offered me a job of a senior lecturer, which I accepted gladly because the teaching load was minimal, sort of seven to eight lecturers, the same seven to eight lectures twice a year and that was the teaching load. The rest of it was research. So that was also a very fruitful period from the research point of view. I came back in 1955 and began working in Bill Paton's department. He was also a great influence on my life. He was thoroughly professional and still is, of course, and he had a team of people a surgeon called Greg Murray, John Thompson, who is now professor of pharmacology in Newcastle, myself, John Gardiner, who went out to be professor of pharmacology in Singapore and is now in the Chinese University, Hong Kong – he became a professional ex-patriot – and Ted Marley, who became another very good friend. He was a psychiatrist who was learning to do behavioural pharmacology and classical pharmacology at the same time. Ted and I did quite a bit of work together. And various odd people coming through, and various visitors... Robert Furchgott from the States, in 1980, after he retired found a new substance secreted by the endothelial cell which he called endothelial-derived relaxing factor, which is suddenly becoming very important. He came and worked there for a couple of months on a sabbatical. So, in all the laboratories I have been in there has always been a tremendous influence from overseas visitors coming to work and bringing fresh ideas and different attitudes.

MB Great surges of ideas, all the time. Tremendous good fortune, but partly chosen, because if you choose to work with Paton, then I suppose that's the natural result. Did you bring histamine back and work on that essentially? Was this the centre of your work there?

JV By that time, I was becoming interested in bioassay, which was Burn's influence, and one of the things that I became interested in, as well as histamine, was 5-hydroxytryptamine. And in 1958, I think it was, I found that if you cut up a bit of rat

[3] William Drummond Macdonald Paton, Professor of Pharmacology, the Royal College of Surgeons, 1954-59; Professor of Pharmacology, Oxford University, 1959-84.

stomach, the fundal part of the rat stomach, into a sort of zigzag strip and hung it up in an isolated organ bath and measured its length, it was very sensitive to contractile activity of 5-hydroxytryptamine. So I published that as a new method for measuring 5-hydroxytryptamine and it became very popular. Later on it turned out that it was also sensitive to prostaglandins and was useful there as a bioassay technique. And then Burn, along with Mike Rand from Australia, began to publish papers suggesting that tyramine and other substances released catecholamines and this was their mode of action. And I began to think of ways in which I could demonstrate unequivocally whether tyramine released catecholamines into the bloodstream rather than simply from the nerve endings onto the actual tissue itself. And one day I thought 'Well, here I am sitting at the bench with the rat's stomach strip bathed in Krebs' solution, which is really just an artificial imitation of the salt constituents of the blood, kept oxygenated, why not use blood itself? And so I anaesthetised a cat and took... and this is where my expertise in perfusion techniques began to play a part because I knew how to handle blood outside the body and how to stop it from clotting and so on. So I took blood and kept it warm and ran it over that stomach strip, recording its length, and back into the cat, gave injections of adrenaline into the cat, and lo and behold when a small part of the blood went round to the rat stomach strip it relaxed in a graded fashion to graded doses. So I began... that was my very first blood-bathed organ and with that it was fairly easy to demonstrate that an injection of tyramine into the bloodstream gave an enormous relaxation of the rat's stomach strip, which I initially interrupted as 'Yes, here's a big release of catecholamines.' But then I began to wonder 'Well, does tyramine have an effect on the rat's stomach strip itself?' So I used reserpinised tissue, which had been... where all of the catecholamines within the rat's stomach had been released and then they didn't relax at all. It became evident that tyramine was indeed causing a release of what turned out to be noradrenaline. It was a local release, locally in the tissues, and not getting into the bloodstream. That began my interest in measuring hormones in the bloodstream by using blood-bathed organs.

MB That had to be a fascinating time.

JV Yes it was, and Bill Paton, a thoroughly professional person, came and looked at my first experiment with obvious disdain. He thought: 'taking blood out of an animal, passing it over a bit of tissue, putting it back in the animal; what are you going

to learn from that?' At least that is what I assume he thought from the expression on his face. He was soon turned round into recognising it was an important method. Having used the rat stomach strip as a blood-bathed organ successfully to show that tyramine didn't release noradrenaline into the bloodstream, but did show it did release it locally in the tissues, I then began to expand my repertoire of isolated organs and began to look for different things that were selectively sensitive to different vasoactive hormones and I found, for instance, that the chick rectum – the rectum of a chick which Gaddum had used – was also highly sensitive to adrenaline but not to noradrenaline, so a combination of these two [bioassays] would distinguish between the two catchecolamines. I had already began to look at 5-hydroxytryptamine in the bloodstream and we begun to look for substances… to find out how they were inactivated in the body. And this led us to look at the lungs and we began to find that the lungs, the pulmonary circulation, has a very powerful mechanism for preventing certain vasoactive hormones from getting into the arterial circulation. They inactivate bradykinin, they inactivate 5-hydroxytryptamine. They take 90 to 95 per cent of the substance out in one circulation time, which is two or three seconds through the pulmonary circulation

MB These must have been colossal findings and very exciting.

JV Very exciting, yes. Now, at some stage, I think it was 1966, Bill Paton left to go to be professor of pharmacology in Oxford and my old friend Gustav Born came to be professor of pharmacology at the Royal College of Surgeons and it was around then that we had a visit from an American called Klaus Unger(?), who also became a firm friend, and he just… he brought with him a little book, the title of which… it was meant for school children for people about to enter university and the book was called a *A Career in Pharmacology*. We had a meeting of the British Pharmacological Society coming to the Royal College of Surgeons and so we decided to do as an after dinner entertainment a spoof on this book, *A Career in Pharmacology*. We borrowed some cameras, we borrowed some… we acquired some 16mm film from friends in ITN [Independent Television News], and in the evenings we would begin to make a film which was directed, produced, camera work by each of us in turn, sort of thing, and we put together a film which is still shown in some laboratories today. I've got a copy of it at home – part of it anyway. And that was a great success. It made everybody laugh. I

played the part of a painter with a palate and a brush and smock and paint all over. My job was to change the kymograph tracings because the man who had obtained the tracings didn't like the rise in blood pressure he got; he wanted a fall in blood pressure. So that was great fun also. And Gus and I had certain disagreements, at midnight usually, because he was new to the chair of pharmacology and he thought of Edith Bülbring seeing the film, and in his imagination everything that went into the film had to be censored so that Edith Bülbring would find it okay, and there was one particular thing which caused a disagreement between us. We had a picture of a rocket being launched from Cape Canaveral which had been supplied by our friends in ITN and the voiceover said, 'The latest invention in pharmacology, a self-inserting suppository,' and Gus didn't like this, he thought that should not go in, and I thought it was great. In the end it went in and caused the biggest laugh of the whole film. We then moved up to the main College of Surgeons in Lincoln's Inn Fields.

MB The whole unit moved?

JV The whole unit moved, they found space for us there and in much better laboratories and it was there that I began to... or continued to do the work on vasoactive hormones and began to gather around me people who have been so supportive in research for the rest of my life. In 1968, no 1967, probably, Priscilla Piper joined me as a graduate student and she brought with her an interest in aspirin and aspirin-like drugs. She had worked with Harry Collier before then. And we had an interest, a joint interest in anaphylaxis in the lungs and so we began to look at the substances released from lungs during anaphylaxis using perfused, isolated lungs from the guinea pig and measuring with my bits of bioassay tissues the stuff coming out, histamine and things. And we had amongst the tissues, a rabbit aorta which usually contracts to many things, but we put antagonists on it so that all of the known substances which it contracted to had no effect, and during anaphylaxis we found this wretched little bit of rabbit aorta contracted. So there was something new there, something which nobody had found before. We also found for the first time – and by this time we had started an interest in prostaglandins – that there was a release during anaphylaxis of E_2 and $F_{2\alpha}$. We called the stuff 'rabbit aorta contracting substance' because that was what it did, and it also stands for Royal College of Surgeons or RCS, and that was a little pun we made. The interest in this was that it only had a very brief life. If you tested the same solution

again three or four minutes later it wasn't there, the activity had disappeared, and we eventually found its release was abolished by aspirin-like drugs. Well, that was the first part of our march towards the mode of action of aspirin, which came a couple of... three years later. We also had a visitor called Sergio Ferreira from Brazil. He came to us in 1966, I think for two reasons: one was to escape trying to organise the Brazilian Pharmacological Congress – he wanted to be outside Brazil while that was going on – and the other was because his wife wanted to work at the London School of Economics. He wanted to work in Oxford with Bill Paton, I think, but since his wife wanted to do a PhD at the LSE he reluctantly came to work with me. We became very good friends.

MB A terrific collaboration.

JV Yes, it sparked off a lot of work. He brought with him in his pocket, an extract of the venom of a Brazilian snake called *Bothrops jaracara* I think it's called the arrowhead viper as well, and he had shown in Rocha e Silva's laboratory... Rocha e Silva discovered bradykinin and Sergio showed in his laboratory that this extract, which he called bradykinin potentiating factor, in fact did that: it potentiated the activity of bradykinin, probably through inhibiting an enzyme which broke down bradykinin. At that time we were working on the renin-angiotensin system as well as on isolated lungs, and I said to Sergio, 'Well, let's test this substance, your extract, on the renin-angiotensin system. We can find out whether it inhibits renin. We can find out whether it inhibits angiotensin converting enzyme.' But science isn't quite like that. He was very wedded to bradykinin and in a week's time I was working with him on bradykinin and not on the renin-angiotensin system. And it took a couple of years before I persuaded another colleague, Mick Bakhle, to look at BPF [bradykinin potentiating factor] on angiotensin converting enzyme, and it was a big inhibitor. Well, the reason for this became clear later on because bradykinin is broken down by the same enzyme, it's broken down by kininase II which is in fact angiotensin converting enzyme. Well, this seemed to us to be a very interesting, exciting discovery that this snake venom would inhibit angiotensin converting enzyme. By this time, my good friend Arnold Welch had moved from Yale to become research and development director at Squibb [Corporation], in Princeton, New Jersey, and he asked me whether I would like to consult with him and I did. It was financially rewarding for a fairly

young person. It was rewarding to go back to the States three times a year, and it was rewarding to go to an active pharmaceutical research organisation and to have an influence on it. Well, I took to them the idea that what they had to do was to purify this snake venom extract because in it clearly was a peptide that inhibited angiotensin converting enzyme and if they could only find this peptide and purify it, they would have a means of testing whether or not angiotensin was important in high blood pressure. The commercial side of the operation were not at all enthusiastic; all they could see was that it is an 'injectable'. 'We don't want an injectable anti-hypertensive drug, we want an oral anti-hypertensive drug.' Arnold Welch was enthusiastic but each time... and they had a man called Miguel Ondetti who was a peptide chemist and who was looking for something to do, and he was very interested. So each time I went back, which was for a week, three times a year, I would have to renew interest to this project. It was beginning to decline, and by the end of my five-day visit they were all enthusiastic about it again. Sergio had gone back to Brazil. He isolated a pentapeptide from this extract, along with a man called Lou Green(?) in New York, and showed that in experimental models of hypertension in the rat that it did cause a fall in blood pressure. Miguel Ondetti isolated a nonapeptide and, under my persuasive influence, reluctantly made a kilogram of this nonapeptide. I had it tested in man. Joe Collier was then working at St George's and he injected the stuff into a man and we showed that it prevented the action of angiotensin I in man, and John Laragh, a famous hypertension man in New York found it did reduce the blood pressure of hypertensives. So the idea that this snake venom might lead to a new drug to lower high blood pressure was beginning to look like a winner. Now, that was in 1972/73 and in early 1973 – and I'm going ahead of myself a bit, because by this time we had done the aspirin work, but I think I'll go on with this – in 1973, John McMichael, who was then a Wellcome trustee phoned me and said, 'John, have you noticed that the Wellcome Foundation (which is a pharmaceutical company which was owned by the Wellcome Trust) the Wellcome Foundation is looking for a R&D [research and development] director. They have been advertising now for six months. Are you interested?' I said, 'No, I'm not interested.' He said 'Well, do me a favour and go and meet the chairman, a man called Andy Gray,[4] and talk to him.' And I did and as a result of that and further talks I became group R&D director of the Wellcome Foundation based in their research

[4] Andrew Aitken Gray, Chairman of the Wellcome Foundation Ltd, 1971-77.

laboratories in Beckenham in Kent. The job was to oversee research and development on a worldwide basis so that also included their laboratories in North Carolina.

MB This involved a colossal enterprise.

JV An enormous enterprise about 3000 people working within research and development. I mean, I was very naive when I went into it. I didn't know the extent of the work that was going on. Andy Gray said, 'Oh, you don't want to go down to the Beckenham labs you've been there before, you've visited there, you don't want to start any rumours going. We'll just assume that everything is okay.'

MB So you went to a very powerful administrative and political field.

JV Yes, and I tried to distinguish between the two. I tried on the one hand to become knowledgeable on a superficial level in all of the different areas of virology, bacteriology, pharmacology, immunology that the Wellcome Foundation were then working on, within its research laboratories, but I still wanted to maintain a very deep interest in my own particular sphere of interest which was the prostaglandins.

End of Part One

The Royal College of Physicians and Oxford Brookes University
Medical Sciences Video Archive MSVA 035

Sir John Vane FRS in Interview with Max Blythe
Oxford, 24 February 1988

Part Two

JV I can now go back to the 1970s and the College of Surgeons. We had found out the mode of action of aspirin. This came about through a series of experiments in the College. With Priscilla Piper, we showed that RCS [rabbit aorta contracting substance] was antagonised... the release of RCS was antagonised by aspirin-like drugs. And then I began to look for the release of RCS *in vivo* and we did dog experiments. We thought that if it comes out of the lungs, maybe we can detect it coming out of the lungs on a piece of rabbit aorta in a blood-bathed organ technique, and maybe we can make the lungs expand and contract more vigorously and maybe we can see some coming out. By then, we thought it was a prostaglandin or related to a prostaglandin, and we knew that prostaglandins were released whenever cells were distorted. So it was fairly natural to over breathe the dog and see if any came out, and we got some RCS coming out, and we gave some aspirin – and we also detected prostaglandins coming out – we gave some aspirin; it didn't seem to do much to the RCS in that situation, but the prostaglandins seemed to go down. Well, at this time there was a whole level of excitement going on in my laboratory. I say my laboratory, it was also Gustav Born's laboratory; we had two groups which interacted very nicely. He ran a group on platelets, I ran a group on cardiovascular work and vasoactive hormones. He did the administration in the department, which wasn't very much: I was left to do my research and get my research grants. One weekend – and there was a tremendous atmosphere of excitement, almost as if we knew something was going to happen – Priscilla Piper was doing her experiments on anaphylaxis in the lungs, we were doing experiments on angiotensin converting enzyme and BPF [bradykinin potentiating factor] inhibition. We were finding that the lungs were important for the conversion of angiotensin I to angiotensin II, which is a prime site of conversion in the endothelial cells of the lungs. We were looking at the fate of different vasoactive hormones in the circulation. We had a great team of people from all over the world, PhD students and visiting fellows.

We'd begun to work on prostaglandins, which we'd first picked up in 1966 in the literature and found that they caused vigorous contractions of bits of gut. So we sent for samples from the Upjohn Company and tested them on our bioassay tissues in case they were interfering with the responses we were getting and began to find bioassay tissue which would pick up the prostaglandins. So we began to look for the release of prostaglandins in the circulation. We found it came out of the spleen. If you stimulate the spleen to contract a whole lot of prostaglandins came out. And the lungs turned out again to be important because they removed or inactivated 98 per cent of any prostaglandin which we then had going through. So we developed the idea, which largely arose from Burn, of local hormones and circulating hormones. A local hormone was something which was released locally, had a function locally and there were mechanisms, enzymic or otherwise, in the bloodstream or in the lungs which would remove it before it had a general effect: circulating hormones, which were meant to circulate and have a general effect. I went home one weekend to write a review, start writing a review, and suddenly things began to fall into place, and on the Monday morning I went back and asked Priscilla Piper and Sergio Ferriera into my office and said, 'I think I know how aspirin works, do you?' I wanted to make very sure I had the idea. 'No,' they said. I said 'Well, I think it prevents the formation of prostaglandins. Everything points to that.' So, I went to the library and found a very simple method described in [E] Änggård and [Bengt] Samuelsson for making a crude prostaglandin synthetase preparation from the very tissue we had been using from the isolated guinea pig lungs. I did my first biochemical experiment, which was to grind up the lungs, make a cell-free supernatant, put it into different test tubes, add the precursor of the prostaglandins, arachidonic acid, and then into some tubes put aspirin, into others put salicylate, into others put morphine as a control, and by the end of the Monday I was convinced that aspirin and salicylate prevented the formation of prostaglandins by an anti-enzymic activity, but morphine didn't, and so the whole thing took off from there. I asked Sergio Ferriera to join me on the project and we had a new graduate student then coming a week later called Salvador Moncada, who is now director of research at Wellcome, and he joined us then and we put together three papers on the mode of

action of aspirin. They were all published simultaneously in *Nature.*[5] I published one on my own on the mechanism of action based upon my anti-enzymic work. With Sergio Ferriera and Salvador Moncada we published one on the spleen, on the release of prostaglandins from the spleen, and we felt it important to show that it wasn't just an anti-enzymic activity but it happened in the whole organ, and later we went on to show that it happened in the whole man as well. And then a PhD student of mine called Jim Willis, who is now back with me for a sabbatical leave for four months, along with his friend Smith, John Smith... I had asked Jim Willis to go off and write up his thesis. I said, 'Jim, I don't want to see you back in the laboratories until you have done some writing.' He was terrible. He never wrote anything up and I thought he was back home, or in the library, busy writing his thesis. Everybody in the lab was excited by my aspirin discoveries, which were then permeating all the way round, and then Jim Willis came in a very nervous fashion and put a paper on my desk and said, 'Smith and I have found that aspirin inhibits the release of prostaglandins from platelets.' I said, 'You're at home writing you thesis.' 'No, no, I've been in working in Gustav's end of the laboratory, unbeknown to you.' He was very nervous. I was rather severe with him and said, 'Well, fine, I'll look at the paper.' It then became important to compare notebooks to find out who had the idea first, which was clearly mine, and they had started about three or four weeks later, but we published those three papers together and they made quite a splash. And [Ulf] von Euler the Nobel Laureate in Finland Physiology or Medicine for his work with [Julius] Axelrod and what's his name[6] on noradrenaline wrote me a letter saying how they had discussed it in his laboratory for two days as he thought it was such important work.

MB What time was this, what was the date…?

JV '71. March '71. I was still at the College of Surgeons and that was a very exciting time.

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[5] Vane, J.R., 1971. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature (New Biol)*, 231, 232-235.

Smith, J.B., and Willis, A.L., 1971. Aspirin selectively inhibits prostaglandin production in human platelets. *Nature (New Biol),* 231, 235-237.

Ferreira, S.H., Moncado, S., and Vane, J.R., 1971. Indomethacin and aspirin abolish prostaglandin release from the spleen. *Nature (New Biol)*, 231, 237-239.

MB Because the core, the real hub of that work…

JV That became the hub or our work, that became the centrepiece because then, although I had hypothesised that aspirin and its similar aspirin-like drugs prevented pain, fever and inflammation by preventing the release of prostaglandins, we then had to do what Dale had to do with all of his mediators, we had to show that prostaglandins were released during inflammation, that they caused the effects that we expected, they caused pain, they caused fever, and, of course, over the next few years, we and others showed all this to be true. We had to show that it happened in whole man and Rob Flower and Joe Collier went off to the loo to provide specimens of semen every so often, because semen contains a lot of prostaglandins and then they took aspirin and found it went down. And so it was a very exciting time. I diverted most of my young people on to the aspirin story. One of the things about being a university professor with ten or fifteen people is that you can change direction very quickly. You can suddenly see an opening and turn the speedboat into the opening and stop and go in a different direction. When I went to Wellcome and gave my first speech there to my co-directors, I compared being a university professor to driving a speedboat, to being the captain of a supertanker where you turn the wheel and waited forever...

MB And this was the role at Wellcome?

JV This was the role at Wellcome, yes.

MB Sir John, I'm going to have to push us on at a reasonable speed to get through the Wellcome [Foundation] years, which were quite important, so can we move into that role now? This is a good time to move into that role and take the early work at Wellcome.

JV Yes, I went to Wellcome. It was a very exciting experience. It meant moving house. My wife and I had been very happy for eighteen years with our kids in Radlett in Hertfordshire, and for the first eighteen months at the Wellcome laboratories at Beckenham in Kent, I travelled to London by train, I was then picked up by a driver at

[6] Ulf von Euler, Julius Axelrod and Sir Bernard Katz shared the Nobel Prize for Physiology or Medicine in 1970 for their discoveries concerning the humoral transmitters in the nerve terminals and the mechanism for their storage, release and inactivation.

St Pancras who took me down, about an hour and half, or hour and forty minutes journey, each way, each day. It helped enormously by my having a driver. I've become accustomed to drivers ever since. Henry Wellcome once said, 'I spend my money on research like others spend it on racecourses.' I spend my money on drivers like others spend it on racecourses. It takes a lot of stress out of life.

MB Did you take the aspirin work across with you? Was this an agreed...?

JV This was one of the reasons that persuaded me to go because by that time we were desperately anxious to try and find some new aspirin-like drugs and we needed an industrial outlet. Squibb I had, but they weren't interested in aspirin-like drugs, they were by that time hell bent to find an orally active anti-hypertensive drug based upon the snake venom work, which they did, three or four years later they found captopril, which became the most successful anti-hypertensive in the field and the first of the angiotensin converting enzyme inhibitors. That was Dave Cushman and Miguel Ondetti who recognised that the nonapeptide out of the snake venom was inhibiting angiotensin converting enzyme, which was a dipeptidase, a small and orally active peptidase which just took off one amino acid, and they then used their knowledge from the snake venom peptides to build a molecule which was orally active. It contained proline like the snake venom peptides, but which inhibited the converting enzyme, and that was a great breakthrough when that happened, of course, after I was no longer consulting with Squibb because I'd gone to Wellcome. So I took with me to Wellcome a nucleus of people interested in prostaglandins. Gerry Higgs was the man who came to set it all up with me. He was the very first and did a magnificent job. He's still there, interested in inflammation and the anti-inflammatory drugs. Part of the excitement of going to Wellcome was to try and develop new anti-inflammatory drugs. What we found very quickly was that if I wanted to change direction, I really had to bring new people in because everybody there had their own problems of research. They had been working on it probably since their PhD thesis. You find among scientists that their PhD thesis sets them on the road for the rest of their scientific careers unless they are very lucky. So people were keeping their heads down, doing their own research, not really interested in helping out the new research director: 'Thank you very much, my stuff's just as important as yours.' So I had to build up my own team of people and I eventually built it up to twenty or so people. Sergio Ferreira

came over for a year to head it and then had to go back to Brazil, Salvador Moncado had by that time received his PhD, gone back to Honduras, which was his home country, to try to set up good science in an underdeveloped country and failed, so he came back and to the Wellcome in 1974, and has been there ever since. He was my right arm as far as my own prostaglandin work went at the Wellcome, and he ran the prostaglandin research group, as it was known then, on a day-to-day basis. Well, under my directorship, over the twelve years that I was at Wellcome, we produced two major drugs: one was acyclovir or Zovirax, which is an anti-herpes drug, the chemistry for which was largely done in the North Carolina laboratory, but the pharmacology and medicine for which was done on both sides of the Atlantic. The other was atracurium or Tracium. The molecule atracurium was first developed by John Stenlake, who was an outside consultant working in a chemistry department up in Scotland. We did the pharmacology in Beckenham and Roy Hughes was the champion of this drug, and eventually it got to the market two or three years before I left Wellcome. And that has turned out to be a winner too. It is selling about £50 million per year now. Zovirax is probably selling more that £200 million a year now, so that was also a winner. Within my own field of expertise, in the schizophrenic personality I had of directing all the research and doing my own science as well, we had come up in 1975/76 with a new prostaglandin. We were beginning to look for thromboxane synthetase inhibitors. By that time, Bengt Samuelson in Sweden had identified what we called RCS, or rabbit aorta contracting substance. He had characterised it chemically and called it thromboxane A_2 and found it was made mainly by platelets. We thought that thromboxane synthetase inhibitors, if they prevented platelets from aggregating together would make good drugs, so we began to look for thromboxane synthetase inhibitors. We began to isolate the enzyme from different tissues. We found it in platelets. We found it in spleen, but we couldn't find it in many other tissues. What diverted our attention away from thromboxane towards something else was that when we incubated the thromboxane precursors with bits of microsomes from rabbit aorta, the activity just disappeared. Now, this meant that either it was being inactivated or that our bioassay tissues were not reactive to a substance that was being made, and it turned out to be the second. There was a substance being made which we detected first on isolated vascular tissues which were able to relax – the rabbit aorta can't relax – and it caused a big relaxation of isolated vascular tissue, and then we found, even more exciting, it inhibited platelet aggregation. So it began to seem that the prostaglandin

cascade, which goes from arachidonic acid to the endoperoxides – which are unstable intermediates – on the one hand... platelets make thromboxane A_2 which causes platelets to come together, causes vasoconstriction; whereas on the other side, the vessel wall makes a different substance which causes relaxation of arteries and which prevents platelets aggregation. I went to Norman Whittaker, who was the head of the prostaglandin chemistry group then – this was in somewhere around about May, 1986 – and said to Norman, 'We've found a new substance, a new prostaglandin. We call it prostaglandin X. We don't know what it is. It is clearly made by the blood vessel wall and is probably important in keeping blood vessels clean, preventing platelets from sticking to them, can you characterise it for us? And by the way, we need it within three months because I think somebody else is on the trail, also, and incidentally it's only got a half-life of two minutes, its very unstable. And Norman very wisely said, 'We don't have the resources.' He said, 'I've only got two prostaglandin chemists and they really couldn't do that kind of job. They're not used to characterising unknown substances.'

MB So you farmed it out?

JV Well, the Upjohn Company is renowned worldwide, or was then, for its prostaglandin chemistry. Wellcome was, then, renowned for its prostaglandin biology. So we took a deputation to Upjohn in Kalamazoo, June 21, 1976, presented them with the work under a confidentiality agreement, because they were rivals of course, and asked them if they would like to join us in a scientific collaboration and they went into caucus for five minutes and came back and said yes, they would. And fairly unique in the pharmaceutical industry, we sent two scientists to their laboratories to help them to characterise prostaglandin X, and by September or October we knew what it was; we knew it had a double ring structure unlike other prostaglandins, and we began to think in terms of finding a name, and we called it prostacyclin. And the patenting and chemical work was such that by December 3, 1976, Salvador Moncada and I were able to go to a meeting in Santa Monica and announce this discovery, which caused quite a few reverberations around the prostaglandin world. So we also followed that up. And there again it was very useful to be within a pharmaceutical company who could develop new drugs. We began to make analogues. We had a five-year scientific agreement with Upjohn to make analogues and we tested them. Other companies

began making analogues too. And then through a series of commercial and political decisions prostaglandins began to receive less emphasis in Wellcome. In actual fact, prostacyclin itself, although it was unstable, has been stabilised by the pharmaceutical and development chemists into a stable preparation and that is now selling two to three million pounds worth a year. So the investment in the prostaglandins wasn't all... has come back.

MB But there were changes in the management at the top at Wellcome at that stage.

JV There were changes in the management at the top.

MB Which led to an uneasy feel...

JV They were feeling that drugs were not coming through the pipeline fast enough. I kept on saying, 'You really have to wait. You know, it takes ten years to develop a drug. We have Zovirax on the way, it'll be here next year. We have atacurium on the way, that'll be next year.' But the pressures were such that they had a much more short-term horizon and it began to be evident that I was at odds with the rest of the board. They had one opinion, I had another.

MB Not an easy time.

JV Not an easy time.

MB This was by about 1979?

JV '79, '80, '81. I was able to maintain, against the board, the research budget, the research and development budget. I was able to maintain the long-term research which we were doing, but after I had decided to resign, within two years there has been cut of 10 per cent in the research budget because it is one of those beasts that when something is in the system they had to get it out of the system, like the dinosaur that takes so long to react. So Salvador Moncada in the last few months has been busy cutting 10 per cent of his head count in research, which is rather like eating you seed corn.

MB Sir John, just taking you through that difficult patch: you decide to leave Wellcome – not an easy thing to go from commanding a team that internationally amounts to three thousand. You really become self-employed and a single spirit, in fact.

JV Of course, by that time I had been to Stockholm in 1982 and that had made a somewhat.... that had changed our life, it had put us into a different orbit, so to speak.

MB Taking a Nobel Prize.[7]

JV Taking a Nobel Prize, yes. And so by 1984, '85 I felt very much more independent than I would otherwise have felt and getting the Nobel Prize probably supported me in my job in Wellcome for an extra two years or so, and allowed me to feel that I was doing a good job there because it brought a lot of kudos to Wellcome. Henry Dale was research director at Wellcome for part of his career and he was a Nobel Prize Winner. I was the second.

MB But all your honours did not always help because I think the knighthood actually caused some speculation as to whether you should be called Sir.

JV Yes, that is a fascinating story. About seven years earlier [before Sir John's knighthood], I was fortunate enough to get Jim Black to come and work with me. He had discovered propanalol, he had discovered cimetidine, and for this work he had been knighted round about 1980, I think it was. Soon after he was knighted, he sent a little memo around to his colleagues saying, 'Within Wellcome I would prefer to remain... be called Dr Black,' and I honoured that. I didn't know why he wanted it, but I honoured it. When my knighthood was announced in '84, the next morning I had a phone call from the chairman saying, 'John, what are you going to be called in Wellcome?' and I said, 'Well, don't know, what do you think?' He said, 'Why don't you go on being called Dr Vane within Wellcome. You know, it would be much better if we did that.' Well, Denis Greenhill, Lord Greenhill, was on the board and he was always a man who knew exactly the right protocol, and I phoned up Denis and said,

[7] Sune K Bergstrom, Bengt I Samuelsson and Sir John Vane shared the Nobel Prize for Physiology or Medicine in 1982 for their discoveries concerning prostaglandins and related biologically active substances.

'Denis, it has been suggested that I shouldn't use the word Sir John.' 'Oh good heavens,' he said 'some people don't do it until they have been dubbed but many people do it from January 1 onwards and yes, of course, you should.' 'Oh no,' I said, 'it wasn't that; it has been suggested that I should be called Dr Vane within Wellcome.' 'Good heavens,' he said 'that would be an insult to the Queen.' So by that time he phoned the chairman and the chairman phoned back and said "forget it"'. But it seemed pretty clear to me then that Jim Black probably had a similar phone call earlier on.

MB And that Shepherd, the chairman, was not happy...

JV He was uneasy having two knights working for him.

MB Two top men.

JV Yes. And that added to the unease, I think. So Jim Black left, I left, Pedro Cuatrecasas the research director in the States left, also. There was an enormous upheaval just before Wellcome went public with its 25 per cent shares. The Trust clearly had to support the chairman in his views, and did so. So the last few years at Wellcome were not an easy time.

MB But, moving away with the Nobel Prize and new freedoms, I can briefly ask – because we don't have a lot of time – I can briefly ask about the excitement of some of the things you have done: Japan, and the number of things you have done that happen to make the intervening six years, five years rather successful.

JV It is a little shorter than that. I left Wellcome in September '85. The first thing I did on leaving was to go to Japan and visit two pharmaceutical companies and two fish oil companies. I have an interest in fish oil. Fish oil contains a substance called eicosapentaenoic acid which can be a precursor of different prostaglandins and it is quite clear that eating fish is healthy and more healthy for you than eating meat. So I fixed up: I got four offers, I fixed up one consultancy with a pharmaceutical company and one with a fish oil company, which I still have. And that became interesting work. I did some legal work with a firm of lawyers in the States. One giant American

pharmaceutical company was suing another over whether Tylenol was better than Brufen or ibuprofen and they were running some knocking adds at the time. So I appeared for the people who were supporting ibuprofen, and that was an interesting time also.

MB A successful defence?

JV Yes.

MB But tell me more about the fish oil.

JV Well, in 1978 a young Dane came to me, called [Jorn] Dyerberg. He had studied Eskimos and said that Eskimos didn't have heart attacks, and he thought it was due to some oil in the fish. By that time it was known that there was eicosapentaenoic acid in fish oil so we did some joint work with him and Salvador Moncada and ourselves and we published a paper in the *Lancet*[8] proposing the hypothesis that eating fish or eating EPA or eicosapentaenoic acid was good for you because it diverted the prostaglandin thromboxane ratio more towards the anti-thrombotic side of things, and that caused a lot of interest and many people are now looking at fish oil and selling fish oil and trying to find products containing fish oil, and the work is still going on. But the general idea that EPA creates a different family of prostaglandins has been recognised. So for six months or so after leaving Wellcome I was very busy consulting with different companies and I was thinking about what I wanted to do and my thoughts crystallised into the idea that I wanted to run a research institute. Working at home is all very well, but you need an infrastructure to keep you active in science, you need to have some young people around to help you to keep an idea of what's going on, and so I began to look round for support. I went to a couple of millionaire friends and looked them in the eyes and said, 'I'm looking for a millionaire who will support me in a new research institute.' One of them said, 'I'm not your man, but I'll give you a £100,000 towards your start up expenses if you want to,' which turned out to be a useful offer, although he forgot it, because a very good friend, David Jack, then the research and development director at Glaxo, phoned me one day and said, 'What are

[8] Dyerberg, J., Bang, H.O., Stofferson, E., Moncado, S., and Vane, J.R., 1978. Eicosapentaenoic acid and prevention of thrombosis and atherosclerosis? *Lancet*, 2:8081, 117-119.

you doing?' and I said, 'Well, I'm looking around for support.' He said, 'Come and have lunch.' We had lunch and he said, 'How much are you looking for? Would half a million pounds a year be enough, do you think?' I said, 'Yes, I think it would.' By that time I had begun negotiations to get laboratory space in St Bartholomew's Hospital Medical School, and to cut a long story short, I am now supported by Glaxo to the tune of half a million pounds per year for five years, with the possibility of going on for eight years in laboratories that have been refurbished and offices which have been built in St Bartholomew's Medical School in Charterhouse Square. And I have a unit now of some twenty five people, including secretaries, which is buzzing with excitement and with new work, and so that is a very happy situation.

MB This is how the Harvey Institute was born.

JV This is how the William Harvey Institute was born. William Harvey was a Bart's man and, and I found to my surprise that Bart's didn't have any William Harvey Institutes, so I created one.

MB And so this the field of maximum activity at present.

JV This is where my main activity is at present. We are looking at atherosclerosis. We want to find out the initiation of atherosclerosis – what are the initiating events. A lot of it is known, but prostacyclin probably plays an anti-atherosclerotic role and EDRF or endothelial derived relaxing factor, which I mentioned earlier, found by Bob Furchgott, probably has a role also. And so we are looking at it in three ways: we are looking at endothelial cells in culture and their interaction with blood cells; we are looking at whole animal experiments and finding models of atherosclerosis; and we are looking at what is released by endothelial cells, using my bioassay cascade system, under a column of endothelial cells that has been grown on beads. So that is all very exciting.

MB Sir John, with that look towards to the future, I'm going to bring this particular interview to a close. I know there are other aspects of your career that are equally fascinating and to which we well return in a further conversation. Thank you very much.